CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020916

MEDICAL/STATISTICAL COMBINED REVIEW(S)

JUN 2 9 1998

Medical and Statistical Review for New Drug Application #20-916

General Information:

Applicant Name:	Astra Merck, Inc.
Applicant's Address:	725 Chesterbrook Blvd., Wayne, PA 19087
Applicant's Telephone:	(610) 695-1008

Submission/Review Dates:

Date of Submission:	September 30, 1997
Date of Receipt:	September 30, 1997
Date Received by Reviewer:	October 1, 1997
Date Review Begun:	February 2 , 1998
Date Review Completed:	June 29, 1998

Drug Identification:

Generic Name	Omeprazole (with amoxicillin and clarithromycin)
Pharmacologic Category:	substituted benzimidazole
Proposed Trade Name:	Prilosec®
Chemical Name:	$C_{17}H_{19}N_3O_3S$
Weight:	345.42
Dosage Form:	Delayed-Release Capsules
Route of Administration:	Oral

Proposed Indication:

"PRILOSEC Delayed-Release Capsules, in combination with clarithromycin and amoxicillin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 5 year history) to eradicate *H. pylori.*

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori.*

Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL PHARMACOLOGY, *Clinical Studies* and DOSAGE AND ASMINISTRATION).

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See the clarithromycin package insert, MICROBIOLOGY section)

Proposed Dosage and Administration:

"H. pylori Eradication for the Reduction of the Risk of Duodenal Ulcer Recurrence: Triple Therapy (PRILOSEC/clarithromycin/amoxicillin): The recommended adult oral regimen is PRILOSEC 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy (PRILOSEC/clarithromycin): The recommended adult oral regimen is PRILOSEC 40 mg once daily plus clarithromycin 500 mg t.i.d. for 14 days. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

Please refer to clarithromycin full prescribing information for CONTRAINDICATIONS and WARNING, and for information regarding dosing in elderly and renally impaired patients (PRECAUTIONS: *General*, PRECAUTIONS: *Geriatric Use* and PRECAUTIONS: *Drug Interactions*).

Please refer to amoxicillin full prescribing information for CONTRAINDICATIONS and WARNINGS."

Related Drugs:
(Indicated for *H. pylori* eradication in patients with duodenal ulcer)
Primary Therapy

- Tritec 400 mg b.i.d. x 4 weeks + Clarithromycin 500 mg t.i.d. for the first 2 weeks
- Omeprazole 20 mg b.i.d. x 2 weeks + Clarithromycin 500 mg t.i.d. x 2 weeks, then Omeprazole 20 mg qd x 2 weeks
- Lansoprazole 30 mg b.i.d x 2 weeks + Clarithromycin 500 mg b.i.d. x 2 weeks + Amoxicillin 1 gram x 2 weeks
- Bismuth Subsalicylate 151 mg q.i.d. + Metronidazole 500 mg b.i.d. + Tetracycline 500 mg q.i.d. + an H_2-receptor antagonist all for 2 weeks

Alternative Therapy

- Lansoprazole 30 mg t.i.d. x 2 weeks + Amoxicillin 1 gram t.i.d. x 2 weeks

Material Submitted: 93 Volumes
Material Reviewed: Volumes 1, and Volumes 6 through 55

Regulatory Background:
Omeprazole has been approved for marketing in the United States since 1989. Current market approvals for omeprazole therapy include the short term treatment of duodenal ulcer (DU) (1989) and gastric ulcer (1995), healing and maintenance of healing of erosive esophagitis (1989 and 1995, respectively), and the long-term management of pathophysiologic hypersecretory conditions (1989). In 1995 it was approved in combination with clarithromycin for the following indication: "...for the treatment of patients with *H. pylori* infection and active duodenal ulcer to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence...". There were two pre-NDA meetings to discuss the submission (March 13, 1997 and July 15, 1997). At the March meeting, concern was expressed that the sponsor may not have enough data to demonstrate a contribution of amoxicillin to the triple therapy regimen (See meeting minutes.) At the July meeting, the sponsor provided data which compared efficacy rates across studies to suggest that the contribution of amoxicillin does not need to be demonstrated again for the current application (See **COMBINATION RULE** section of this review).

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BACKGROUND ON INDIVIDUAL AGENTS

Omeprazole: Omeprazole is supplied as 10- and 20- mg capsules. The usual daily dose for most indications is 20 mg, although daily doses of up to 360 mg have been administered for hypersecretory conditions. The typical duration for most acute conditions is 4 to 8 weeks. Some patients with Zollinger-Ellison syndrome have been treated continuously with omeprazole for more than 5 years.

Omeprazole can inhibit *H. pylori* growth *in vitro* at relatively high concentrations. It can also apparently reduce the population of *H. pylori* colonizing the gastric antrum to the extent that the organisms may not be detected on gastric biopsy during omeprazole therapy. This clearance is transient, however, and *H. pylori* colonization returns to pretreatment levels after omeprazole has been discontinued.

Amoxicillin: Amoxicillin is a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is currently approved for the treatment of infections due to susceptible strains of certain gram-positive and gram-negative bacteria. The recommended adult daily dose varies from 750 mg to 1.5 gm depending on the location of the infection and the susceptibility of the organism. These doses are typically given for 10 days. The maximal daily oral dose is 3 gm (for gonorrhea).

H. pylori is highly susceptible to amoxicillin *in vitro* and resistance to amoxicillin in the U.S. has not yet been reported in published studies.

Clarithromycin: Clarithromycin is a semi-synthetic macrolide antibiotic with very high activity against *H. pylori* in vitro. It is currently approved for a number of infections. Dosing is typically for 10 days. Most current *H. pylori* regimen with increase activity include clarithromycin as one of the components.

Overview of Phase 3 Studies

Tables 1, 2, and 3 summarizes the clinical features, medication dosing, and diagnostic criteria for the phase 3 clinical studies including O + A therapy, O + C therapy, and O + A + C therapy.

Table 1
Summary of *H. pylori* Studies

	Diagnosis (in addition to *H. pylori* infection)	Timing of *H. pylori* Eradication Status Assessment	Timing of Duodenal Ulcer Status Assessment	Treatment Groups †	Number of Days for Regimen	Additional Therapy for Ulcer Healing †
O+A+C Studies						
126	Active duodenal ulcer	4 weeks post-therapy	4 weeks post-therapy	O + A + C	10	O for 18 days
				A + C	10	placebo
127	Active duodenal ulcer	4 weeks post-therapy	4 weeks post-therapy	O + A + C	10	O for 18 days
				A + C	10	placebo
M96-446	Duodenal ulcer diathesis without active crater	4 to 6 weeks post-therapy	4 to 6 weeks post-therapy	O + A + C	10	none
				A + C	10	none
O+A Studies						
035	Active duodenal ulcer	4 weeks post-therapy	4 weeks post-therapy	O + A	14	O for 14 days
				O	14	O for 14 days
				A	14	placebo
036	Duodenal ulcer diathesis without active crater	4 weeks post-therapy	4 weeks post-therapy	O + A	14	none
				O	14	none
				A	14	none

† O = omeprazole, A = amoxicillin, C = clarithromycin

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Table 1 (continued)

	Diagnosis (in addition to *H. pylori* infection)	Timing of *H. pylori* Eradication Status Assessment	Timing of Duodenal Ulcer Status Assessment	Treatment Groups †	Number of Days for Regimen	Additional Therapy for Ulcer Healing †
O+C Studies						
M93-067	Active duodenal ulcer	4 to 6 weeks post-therapy	end of therapy (Week 4), 4 to 6 weeks post-therapy, 3 months, and 6 months	O + C	14	O for 14 days
				O	14	O for 14 days
				C	14	placebo
M93-100	Active duodenal ulcer	4 to 6 weeks post-therapy	end of therapy (Week 4), 4 to 6 weeks post-therapy, 3 months, and 6 months	O + C	14	O for 14 days
				O	14	O for 14 days
				C	14	placebo
O+A+C vs. O+C Study						
M94-183	Active duodenal ulcer	4 to 6 weeks post-therapy	4 to 6 weeks post-therapy (also at end of therapy in France)	O+A+C	10	none
				O+C	14	none

† O = omeprazole, A = amoxicillin, C = clarithromycin

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Table 2
Summary of *H. pylori* Study Medication and Doses Used in the Studies

	Treatment Group	O †	A †	C †	Number of Days for Regimen	Additional Therapy for Ulcer Healing †
O+A+C Studies						
126	1	20 mg bid	1 g bid	500 mg bid	10	O 20 mg qd for 18 days
	2	placebo bid	1 g bid	500 mg bid	10	placebo
127	1	20 mg bid	1 g bid	500 mg bid	10	O 20 mg qd for 18 days
	2	placebo bid	1 g bid	500 mg bid	10	placebo
M96-446	1	20 mg bid	1 g bid	500 mg bid	10	none
	2	placebo bid	1 g bid	500 mg bid	10	none
O+A Studies						
035	1	20 mg bid	1 g tid	none	14	O 20 mg qd for 14 days
	2	20 mg bid	placebo tid	none	14	O 20 mg qd for 14 days
	3	placebo bid	1 g tid	none	14	placebo
036	1	20 mg bid	1 g tid	none	14	none
	2	20 mg bid	placebo tid	none	14	none
	3	placebo bid	1 g tid	none	14	none

† O = omeprazole, A = amoxicillin, C = clarithromycin

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Table 2 (Continued)
Summary of *H. pylori* Study Medication and Doses Used in the Studies

	Treatment Group	O †	A †	C †	Number of Days for Regimen	Additional Therapy for Ulcer Healing †
O+C Studies						
M93-067	1	40 mg qd	none	500 mg tid	14	O 20 mg qd for 14 days
	2	40 mg qd	none	placebo tid	14	O 20 mg qd for 14 days
	3	placebo qd	none	500 mg tid	14	placebo
M93-100	1	40 mg qd	none	500 mg tid	14	O 20 mg qd for 14 days
	2	40 mg qd	none	placebo tid	14	O 20 mg qd for 14 days
	3	placebo qd	none	500 mg tid	14	placebo
O+A+C vs. O+C Study						
M94-183	1 ‡	20 mg qd	1 g bid	500 mg bid	10	none
	2 ‡	40 mg qd	placebo bid	500 mg tid	14	none

† O = omeprazole, A = amoxicillin, C = clarithromycin

‡ In Study M94-183, double dummy drug therapy was used for this double-blind study. Patients received appropriate placebo matching therapy in order to blind the study.

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Table 3. Summary of *H. pylori* Diagnostic Tests Used in the Studies

	CLOtest®	Histology	Culture	^{13}C-UBT	Determination of *H. pylori* Infection at Baseline	Determination of *H. pylori* Eradication Status at 4 to 6 Weeks Post-Therapy
O+A+C Studies						
126	√	√	√		culture positive **or** CLOtest® positive and histology positive	no test positive and at least two tests negative
127	√	√	√		culture positive **or** CLOtest® positive and histology positive	no test positive and at least two tests negative
M96-446	√	√	√		culture positive **or** CLOtest® positive and histology positive	no test positive and at least two tests negative
O+A Studies						
035	√	√	√		CLOtest® positive **and** either histology or culture positive	no test positive and at least two tests negative
036	√	√			CLOtest® positive **and** histology positive	both tests negative
O+C Studies						
M93-067	√ baseline only	√	√	√	Either histology **or** culture positive (CLOtest® required to be positive for study entry)	no test positive and at least one test negative
M93-100	√ baseline only	√	√	√	Either histology **or** culture positive (CLOtest® required to be positive for study entry)	no test positive and at least one test negative
O+A+C vs. O+C Study						
M94-183	√ baseline only	√	√	√	Either histology **or** culture positive (CLOtest® required to be positive at entry)	no test positive and at least one test negative

MEDICAL AND STATISTICAL REVIEW OF STUDY 126

INVESTIGATORS

Thirty (30) primary investigators participated in the trial. Their facilities and locations are listed in Table 4. This study was conducted by on behalf of Astra Merck Inc. is a Contract Research Organization (CRO) located in The study used three central laboratories. All laboratory safety tests (blood chemistry, hematology and urinalysis) were performed by located in . All gastric biopsy specimens were sent to the laboratories of David Y. Graham, M.D., Baylor University, Houston, Texas for microbiological or histological assessment of *H. pylori* and antibiotic susceptibility.

Statistical Reviewer's Comment: Several of the investigators for this trial were also involved in Abbott study 56268 (e.g., Drs. Lanza, Movva, Shah, and Wruble). It is unclear whether any patients enrolled in this study by these investigators were also enrolled at a different timepoint in the Abbott study.

Whenever there is overlap of investigators between studies, one questions whether the trials can be deemed independent as we would like them to be. However, there is no overlap of investigators between studies 126 and 127, so we do have two independent trials of this therapy for this indication.

TABLE 4
List of Investigators
Study #126

Primary Investigator	Site #	Facility	Location
E. David Ballard II, M.D.	015	Private Practice	2800 Winslow Avenue Suite 202 Cincinnati, OH 45206
Charles F. Barish, M.D.	001	Wake Research Associates, Inc.	3100 Blue Ridge Road Suite 100 Raleigh, NC 27612
Malcolm Berenson, M.D.	021	University Medical Center, GI Division	50 North Memorial Drive Room 4R 118 Salt Lake City, UT 84132
Antonio Caos, M.D.	010	Private Practice	11140 West Colonial Drive Ocoee, FL 34761
Carl DeAbate, M.D.	004	Medical Research Center	1020 Gravier Street Suite 100 New Orleans, LA 70112
Timothy B. Deering, M.D.	025	Partners Research Clinic	390 South French Broad Avenue Ashville, NC 28801
Daniel G. Fagel, M.D.	018	Private Practice	196 Barnwood Drive Edgewood, KY 41017
M. Brian Fennerty, M.D.	022	Oregon Health Sciences University	Gastroenterology, PV-310. 3181 S.W. Sam Jackson Park Road Portland, OR 97201
C.L. Fisher, M.D.	024	Private Practice	813 Diligence Drive Suite 109 Newport News, VA 23606
Syam Gaddam, M.D.	028	Private Practice	1751 West Romneya Drive Suite J Anaheim, CA 92801
Neil Hirschenbein, M.D.	020	Affiliated Research	8880 Rio San Diego Drive #1090 San Diego, CA 92108
David S. James, M.D.	029	Private Practice	3345 South Harvard Suite 301 Tulsa, OK 74135

TABLE 4 (cont.)
List of Investigators
Study #126

Primary Investigator	Site #	Facility	Location
Rokay Kamyar, M.D.	009	Private Practice	6699 Alvarado Road, # 2309 San Diego, CA 92120
Paul King, M.D.	017	University of Missouri Medical Ctr	N425 HSC Clinical Research Unit One Hospital Drive Columbia, MO 65212
David Kogut, M.D.	002	Piedmont Gastroenterology	1835 Davie Avenue Statesville, NC 28677
Kenneth Kohagen, M.D.	016	Raleigh Internal Medicine	3320 Wake Forest Road Raleigh, NC 27609
Frank L. Lanza, M.D.	011	Houston Institute for Clinical Research	7777 S.W. Freeway # 700 Houston, TX 77074
William Martin, M.D.	006	Fayetteville Diagnostic Clinic	3344 North Futrall Drive Fayetteville, AR 72703
Paul Maton, M.D.	008	Oklahoma Foundation for Digestive Research	700 N.E. 13th Street Oklahoma City, OK 73104
David Morris, D.O.	012	Healthcare Research Consultants	4619 South Harvard Suite 4 Tulsa, OK 74135
Rao V. Movva, M.D.	003	Private Practice	545 Valley View Drive Moline, IL 61265
John Ondrejicka, M.D.	030	Health Trials 3000	2380 South Third Avenue Jacksonville Beach, FL 32250
George Pyke, M.D.	005	Clinical Studies, Orlando	695 Douglas Avenue Altamonte Springs, FL 32714
Jeffrey Rosen, M.D.	013	Clinical Research of Southern Florida	299 Alhambra Circle Coral Gables, FL 33134
Umedachandr Shah, M.D.	007	Shanti Medical Center	P.O. Box 664 Leonardtown, MD 20650
Reza Shaker, M.D.	023	Froedtert Memorial Lutheran Hospital	9200 West Wisconsin Avenue Milwaukee, WI 53226
David Sloas, M.D.	019	Methodist Hospital of Memphis	1265 Union Avenue - 107 Sherard Memphis, TN 38104

TABLE 4 (continued)
List of Investigators
Study #126

Primary Investigator	Site #	Facility	Location
Peter J. Winkle, M.D.	026	Associated Gastroenterology Medical Group	2617 East Chapman Avenue Suite 302 Orange, CA 92669
Barry Winston, M.D.	027	Private Practice	800 Peakwood Drive Suite 5D Houston, TX 77090
Lawrence Wruble, M.D.	014	Mid South Clinical Research Institute	80 Humphrey's Center Suite 220 Memphis, TN 38120

STUDY OBJECTIVES

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Primary Objectives

- To assess the efficacy of a ten day treatment regimen of omeprazole, amoxicillin and clarithromycin on eradication of *H. pylori* in patients with acute duodenal ulcer and *H. pylori* infection.
- To assess the tolerability of a ten day treatment regimen of omeprazole, amoxicillin and clarithromycin in patients with acute duodenal ulcer and *H. pylori* infection.

Secondary Objectives

- To assess the efficacy of a ten day treatment regimen of omeprazole, amoxicillin and clarithromycin on duodenal ulcer healing in patients with acute duodenal ulcer and *H .pylori* infection.
- To assess the efficacy of a ten day treatment regimen on the combined endpoint of *H. pylori* eradication and duodenal ulcer healing.
- To demonstrate that eradication of *H. pylori* leads to higher healing rates of duodenal ulcer.
- To assess the rate of three antimicrobial agents (amoxicillin, clarithromycin and metronidazole) resistance among *H. pylori* isolates from patients before and after study treatment.
- To assess the relationship between treatment groups in the time until patient is free of ulcer symptoms.

- To assess the relationship between *H. pylori* eradication results based on histology, results based on CLOtest®, and results based on culture at baseline and also at the Week 8 visit.

INVESTIGATIONAL PLAN

This was an 8 week, randomized, multicenter, double-blind, parallel group study. *H. pylori* infected patients with one or more endoscopically confirmed duodenal ulcer(s) were randomized to one of the following two treatment regimens for ten days:

1. omeprazole 20 mg bid + amoxicillin 1 g bid + clarithromycin 500 mg bid (85 patients planned)

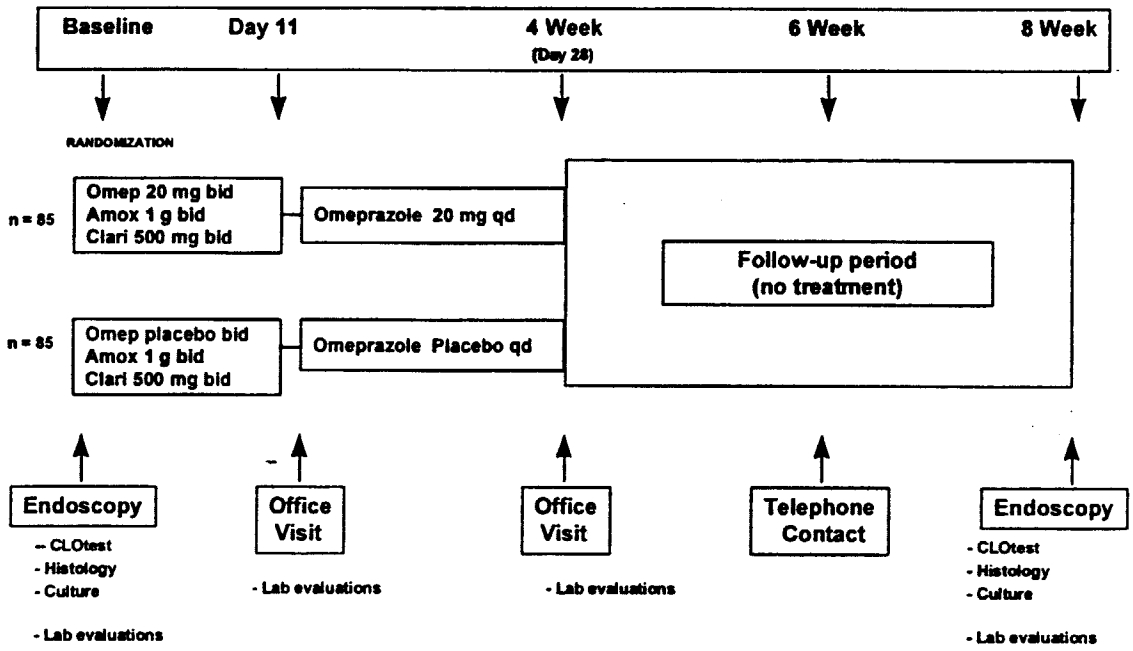
2. omeprazole placebo bid + amoxicillin 1 g bid + clarithromycin 500 mg bid (85 patients planned)

After 10 days of treatment, patients in treatment group 1 received an additional 18 days of omeprazole 20 mg qd. Patients in treatment group 2 received an additional 18 days of omeprazole placebo qd. As patients were randomized, they were stratified by smoking history. All patients were given GELUSIL® antacid to take as needed for symptom relief. *H. pylori* status was assessed at baseline and Week 8 using CLOtest®, histology and culture. In addition, the *in vitro* culture samples were used to assess the susceptibility of *H. pylori* to antimicrobial agents. Duodenal ulcer status was assessed endoscopically at baseline and Week 8. During the study, the severity of ulcer symptoms was recorded daily by the patient on a diary card. Adverse events were recorded throughout the study. Routine laboratory safety tests were performed at baseline, Day 11 and Weeks 4 and 8. Study assessments were performed according to the schedule in Figure 1.

Statistical Reviewer's Comment: Patients were stratified by smoking status before being randomized to treatment. The primary analysis adjusts for smoking status. Eradication rates appear somewhat lower for smokers but not markedly so (differences are not statistically significant).

SCHEDULE OF VISITS

The schedule of visits for Astra-Merck Study 126 is outlined below:



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INCLUSION CRITERIA

- Males or females (either post menopausal or using reliable means of contraception), aged 18 years or older.
- Evidence of *H. pylori* infection at baseline via a positive CLOtest® within 6 hours from the time the CLOtest® was started.
- Endoscopic documentation of one or more duodenal ulcer(s), 0.5 to 2.5 cm in diameter, not more than 3 days prior to the start of study medication. No duodenal ulcer could be larger than 2.5 cm in diameter.

EXCLUSION CRITERIA

- Patients with organic pyloric obstruction, prepyloric ulcer, pyloric channel ulcer, gastric ulcer, erosive esophagitis, Barrett's esophagus at the baseline endoscopy.
- Patients who may have had Zollinger Ellison Syndrome.

- Patients with a history of refractory duodenal ulcer: patients with a duodenal ulcer that failed to heal after 12 weeks of full dose therapy with H_2-receptor antagonists or 4 weeks of proton pump inhibitors treatment.
- Patients with active GI bleeding at baseline visit. Bleeding disorders included coagulation disorders of all types such as the need for administration of anticoagulants. Any patient with a bleeding disorder with endogenous and/or iatrogenic conditions was excluded from the study.
- A risk of clinically significant gastrointestinal bleeding as judged by the investigator.
- Patients who had taken daily continuous treatment with any dose of the following medications in the two months prior to the endoscopy screening visit: proton pump inhibitors, oral, intravenous, or intramuscular antibiotics and bismuth containing compounds.
- Need for continuous concurrent therapy with: antibiotics with antimicrobial therapy effective against *H. pylori*, anticholinergics, prostaglandin analogs, antineoplastic agents, salicylates (unless ≤165 mg daily for cardiovascular prophylaxis), bismuth compounds, H_2-receptor antagonists, steroids (oral or intravenous), pro-motility drugs, sucralfate, nonsteroidal anti-inflammatory drugs, theophylline, anticoagulants including warfarin sodium (Coumadin®) and heparin.
- The use of terfenadine (Seldane® and Seldane-D®) and/or cisapride (Propulsid®) and or pimozide (Orap®) was prohibited one week prior to, during and one week after treatment.
- The use of astemizole (Hismanal®) was prohibited two weeks prior, during and two weeks after treatment.
- The use of diazepam, phenytoin, digoxin, disulfiram, propafenone or carbamazepine unless the patient was adequately monitored.
- The use of quinidine, disopyramide phosphate (Norpace®) and nefazodone hydrochloride (Serzone®).
- The use of amiodarone (Cordarone®) 4 months prior and during the study.
- Patients with known hypersensitivity to any component of omeprazole, amoxicillin, clarithromycin, penicillin or GELUSIL®.
- Patients who were taking an investigational drug or those who had taken an investigational drug within 2 months of the baseline visit.
- Patients who were participating or who had participated in the Astra Merck Study 127.
- Current or historical evidence (within 3 months) of any of the following diseases/conditions: pancreatitis; malabsorption; inflammatory bowel disease; severe pulmonary or liver disease; renal disease or impaired renal function (as

manifested by any of the following: creatinine clearance <50 ml/min., serum creatinine greater than 2.0 mg/dl or markedly abnormal urine sediment on repeated examinations); active malignant disease except minor superficial skin disease; unstable diabetes mellitus (stable diabetics controlled on diet, oral agents or insulin were acceptable); clinically significant untreated or ineffectively treated systolic and/or diastolic (>110 mmHg) hypertension, unstable heart disease (e.g., myocardial infarction, congestive heart failure or serious arrhythmias); (occasional premature ventricular contractions did not exclude a patient from the study; patients with heart disease had to be classified by the New York Heart Association criteria as being in Functional Class I or II); cerebral vascular disease, such as cerebral ischemia, infarction, hemorrhage, or embolus; any bleeding disorder; any condition that required inpatient surgery during the study.

- Patients who were considered by the investigator to be alcoholics not in remission or known substance abusers.
- Clinically significant abnormal laboratory values for any prestudy laboratory test.
- Patients with a positive serum pregnancy test.

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PATIENT REMOVAL

Investigators were permitted to discontinue a patient from the study because of noncompliance, the development of adverse events, or the judgment that the patient required additional therapy for his or her duodenal ulcer. At the time of withdrawal, the date and reason for withdrawal were recorded. Investigators were instructed to consider patients non-compliant due to either lack of attendance at scheduled visits, if they were lost to follow-up, or for violations of the protocol.

Medical Officer's comment: The term "noncompliance" used by the sponsor is inclusive of more patients that just those who were documented to not take medication based on pill count. Patients who were lost to follow-up, did not attend scheduled visits, or who had violations of the protocol were considered non-compliant even if the reason for withdrawal was unrelated to study medication. The specific reason for "non-compliance" was considered in making patient assessments by the MO.

OTHER STUDY DESIGN FEATURES

Patients were stratified by smoking history at randomization. Open label GELUSIL® tablets were provided for all patients. Treatment compliance was measured diary cards and pill counts.

DIAGNOSTIC METHODS

The presence of *H. pylori* was assessed at baseline and Week 8 via the CLOtest®, histology and culture using gastric biopsies. Duodenal ulcer status was also assessed during the endoscopic examinations at baseline and Week 8. During both endoscopic examinations, gastric mucosal biopsies (4 antral; 3 corporeal) were collected using large-cup forceps, or alternatively, using a standard forceps with an elliptical cup. One antral biopsy was used for the CLOtest®. Two antral and two corporeal biopsies were used for histological assessment of *H. pylori*. One antral and one corporeal biopsy were used for bacteriological culture of *H. pylori* and subsequent antimicrobial susceptibility testing (for amoxicillin, metronidazole, clarithromycin) when *H. pylori* was present. Agar dilution and the Etest®
were used to assess the susceptibility of *H. pylori* to the antimicrobials.

ULCER HEALING STATUS AT WEEK 8

Healed Duodenal Ulcer Complete epithelialization of duodenal ulcer(s) and erosions present at baseline. New erosions remote from index ulcer site were permitted.

Unhealed Duodenal Ulcer Duodenal ulcer(s) was still present (ulcer sharply circumscribed, three-dimensional lesion with a white base).

Erosion: Erosions observed at the baseline endoscopy were still present. Erosion at the site of the index ulcer was considered an unhealed duodenal ulcer.

GI SYMPTOM ASSESSMENT

At the baseline visit, patients were asked to assess their global day and night ulcer symptoms for the 7-day period prior to the baseline visit. During the 4 week treatment period, patients were also asked to record in diaries, on a daily basis, the degree of severity for their day and night ulcer related symptoms.

Patients evaluated day and night symptoms as follows:

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Day Symptoms

None -- No ulcer-related symptoms.

Mild -- Bothered a little; symptoms are present part of the day but cause little or no discomfort.

Moderate -- Bothered to some degree; symptoms are present most of the day, annoying, but not interfering with daily routine.

Severe -- Bothered intensely; constant ulcer symptoms causing marked interference with daily routine.

Night Symptoms

None -- No ulcer-related symptoms.

Mild -- Bothered a little; symptoms are present part of the night, do not interfere with sleep.

Moderate -- Bothered to some degree; symptoms are present most of the night, occasionally interferes with sleep.

Severe -- Bothered intensely; constant ulcer-related symptoms causing marked interference with sleep.

EFFICACY ASSESSMENTS

Primary Efficacy Parameter:

***H. pylori* Infection and Eradication**

A patient was considered to be infected with *H. pylori* at baseline if a positive CLOtest® was confirmed by positive histology or a patient was considered to be infected if culture was positive for *H. pylori* (i.e., culture isolated *H. pylori).*

At Week 8, a patient was considered to have the *H. pylori* infection eradicated if no test result was positive and at least two of the test results were negative (CLOtest®, histology, culture). If at least one test demonstrated the presence of *H. pylori* at Week 8, the patient was considered to still be infected (i.e., *H. pylori* not eradicated), regardless of the number of interpretable test results.

For histology and culture, both antrum and corpus biopsies were tested. If at least one of the biopsies (antrum or corpus) was positive, the patient was considered to be positive for *H. pylori* for that particular test. If only one biopsy (either antrum or corpus) had interpretable results for a given test, the results of that biopsy determined the result for that particular test. For culture, if the biopsy sample was classified as not sufficient by the pathologist, and *H. pylori* isolates were reported as not present, that biopsy sample was considered to be not interpretable. However, if *H. pylori* isolates were reported as present, the biopsy sample was considered to be positive for *H. pylori*, whether or not the biopsy was considered to be sufficient.

Medical Officer's Comments: The definitions of H. pylori infection and eradication are consistent with the Division's guidance and recommendations. The use of three endoscopic tests post-treatment (rather than two) makes the eradication assessment more conservative than that suggested by the Division.

Secondary Efficacy Parameters

1. Duodenal ulcer healed status by Week 8 was classified as either "not healed" or "healed" (no duodenal ulcer present, and no erosions at original site of ulcer)

2. Time until patient is free of ulcer symptoms was determined by the number of days until the patient records a no symptoms for both day and night ulcer symptoms and continues to be symptom free through Study Day 28. If day and night ulcer symptoms were never "none" then time until patient is free of ulcer symptoms was assigned as the last study day where the patient recorded having at least "mild" day and/or night ulcer symptoms (i.e., a censored value). Only patients with mild to severe baseline global ulcer symptom scores for either day or night symptoms were included in this analysis.

3. Number of GELUSIL tablets taken throughout the study period

The average daily usage of GELUSIL® antacid tablets was summarized for each patient throughout the first 4 weeks of the study (Study Days 1 through 28).

4. Study Drug Usage

A patient who had taken at least 75% of the prescribed doses of each study medication and had not missed more than 3 consecutive days of study medication within the first 10 days of the study treatment period (Study Days 1 through 10), and who also had not missed more than 6 days of study medication within the next 18 days (Days 11 through 28), was considered to be compliant. The diary card data were used to make this assessment.

5. Susceptibility of *H. pylori* by Etest®

Susceptibility testing of all the *H. pylori* isolates in this study was conducted by a central laboratory using the Etest®. The susceptibility of the *H. pylori* isolates to amoxicillin, clarithromycin, and metronidazole was determined at baseline and Week 8 for each patient based on Minimum Inhibitory Concentration (MIC) values from the Etest®. The MIC value Etest® breakpoints used in this study to determine the susceptibility status of the *H. pylori* isolates are listed below for amoxicillin and clarithromycin. Breakpoints were determined for this study by observing the baseline MIC value distributions for the *H. pylori* isolates in this study based on Etest® results according to *H. pylori* eradication status at Week 8.

Minimum Inhibitory Concentration (MIC) Breakpoints from Etest® for Determining *H. pylori* Susceptibility Status

Study #126

Susceptibility Status	Amoxicillin	Clarithromycin
Resistant	Undefined	MIC > 2 mcg/ml
Intermediate	Undefined	0.125 mcg/ml< MIC ≤ 2 mcg/ml
Susceptible	MIC ≤ 0.38 mcg/ml	MIC ≤ 0.125 mcg/ml

Susceptibility of *H. pylori* by Agar Dilution

Susceptibility testing of a subset of the *H. pylori* isolates was conducted by a central laboratory using agar dilution. The susceptibility of the *H. pylori* isolates to amoxicillin and clarithromycin was determined for this subset of isolates at baseline and Week 8 based on Minimum Inhibitory Concentration (MIC) values from agar dilution. The MIC value agar dilution breakpoints used in this study to determine the susceptibility status of the *H. pylori* isolates are listed in below for amoxicillin and clarithromycin.

Minimum Inhibitory Concentration (MIC) Breakpoints from Agar Dilution for Determining *H. pylori* Susceptibility Status

Susceptibility Status	Amoxicillin	Clarithromycin
Resistant	Undefined	MIC > 2 mcg/ml
Intermediate	Undefined	0.25 mcg/ml< MIC ≤ 2 mcg/ml
Susceptible	MIC ≤ 1 mcg/ml	MIC ≤ 0.25 mcg/ml

STATISTICAL ANALYSES AND EVALUABILITY CRITERIA

H. pylori Eradication

The sponsor's primary statistical analysis of all efficacy data was performed using a "per-protocol" patient population (i.e., an "evaluable" patient population). Results were also examined for a "modified intention-to-treat" patient population.

Medical Officer's Comments: The "modified intent to treat" (MITT) population is referred to as the ITT analysis throughout this review. The definition was consistent with the Division's guidance although patients also had to have received 1 dose of study medication to be included in this population.

For both patient populations, patients were analyzed according to the study treatment that was actually given to the patient to take. Exclusion of patient data from both analyses was determined before the treatment group allocation was unblinded.

Statistical Reviewer's Comment: To maintain the randomization, patients should have been analyzed with the treatment group to which they were randomized, rather than with the treatment group they actually ended up in (in accordance with the "intent-to-treat" principle). In this study, however, there were no patients who were randomized to one treatment and ended up receiving another treatment.

This comment also applies to study 127 (again, in study 127, no patients ended up receiving an incorrect treatment course).

"Per-Protocol" (PP) Population

Patients were included in the "per-protocol" analysis for both *H. pylori* eradication analysis and ulcer healing analysis as long as they did not violate any of the following conditions:

Criteria A. *H. pylori* was documented as positive based on the positive results of a baseline CLOtest® (rapid urease test) and confirmed by positive results of histology **or** *H. pylori* was documented as positive based on the positive results of culture. Biopsies for these tests could be taken no more than 10 days prior to the first day of study medication.

Criteria B. Baseline endoscopy documented at least one duodenal ulcer, 0.5 to 2.5 cm in diameter, no more than 10 days prior to the first day of study medication.

Criteria C. Patient did not receive more than 5 days of oral, intravenous or intramuscular antimicrobial therapy or bismuth compounds and did not receive any proton pump inhibitors within 4 weeks prior to the first dose of study medication.

Criteria D. Patient took at least 75% of the prescribed doses of study medication (for each of the three study drugs) and did not miss more than 3 consecutive days of study medication within the first 10 days of the study treatment period (Study Days 1 through 10).

Criteria E. Patient did not receive any non-study oral, intravenous or intramuscular concomitant antimicrobial therapy or bismuth containing compounds throughout the 8 week study period.

Statistical Reviewer's Comment: It would be preferable to include patients who received such therapy in the analysis as evaluable failures if their therapy was due to treatment failure. There were only 3 patients receiving concomitant therapy in each arm, however, so results would not differ greatly or lead to any changes in the regulatory decision.

Criteria F. Patient did not receive more than 5 days of any H_2-receptor antagonist and had not received any non-study proton pump inhibitors or sucralfate throughout the 8 week study period.

Criteria G. Patient returned for the final endoscopy office visit and had efficacy measures taken. In addition, a patient was considered not evaluable if the patient had any of the following exclusion criteria as stated in the protocol:

Criteria H. - The patient was suspected to have Zollinger-Ellison syndrome or the patient had current evidence of pancreatitis, malabsorption, inflammatory bowel disease,

- severe pulmonary, renal or liver disease, or unstable diabetes mellitus or

- the patient was considered by the investigator to be an alcoholic not in remission or a known substance abuser.

To consider a patient to have the *H. pylori* infection eradicated, testing for *H. pylori* status must have been performed at least 4 weeks after the end of therapy. If a patient had no available data or did not have the appropriate number of interpretable test results at Week 8 (within day range for that time point), the patient was not included in the analysis of *H. pylori* eradication.

If a patient had a healed duodenal ulcer at any time during the 8 week study period on or after Study Day 1, the patient was considered to have a healed duodenal ulcer by Week 8. If a patient had a healed duodenal ulcer on or after Study Day 1, but an unhealed ulcer on at least one visit on or after Study Day 29, the patient was considered to have an unhealed duodenal

ulcer. However, a patients who had a healed duodenal ulcer and had no available data on or after Study Day 29, were not included in the per-protocol ulcer healing analysis.

Medical Officer's Comments:

These per-protocol evaluability criteria were similar to those presented in the DAIDP (Draft) Evaluability Criteria Document except that the guidance document makes the following recommendations:

- Compliance was defined as 80% of study medications

- Concurrent antimicrobial use is considered as a reason for making a patients " non-evaluable"

- Patients who withdraw from the study are considered "evaluable failures" if the reason for withdrawal is related to study medication or presumed progression of the disease. Dropouts are considered unevaluable if the reason for withdrawal is unrelated to the study medication or the primary disease process. This becomes most important when patients drop out of the study because they develop an adverse event that is possibly or probably related to the study medication.

"Intention-to-Treat" (ITT) *H. pylori* Eradication Patient Population

Patients were included in this analysis as long as they had not violated any of the following conditions.

Criteria A. *H. pylori* was documented as positive based on the positive results of a baseline CLOtest® (rapid urease test) and confirmed by positive results of histology **or** *H. pylori* was documented as positive based on the positive results of culture. Biopsies for these tests could be taken no more than 10 days prior to the first day of study medication.

Criteria B. Baseline endoscopy documented at least one duodenal ulcer.

Criteria C. Patient took at least one dose of study medication.

To consider a patient to have the *H. pylori* infection eradicated, testing for *H. pylori* status must have been performed at least 4 weeks after the end of therapy. Thus, the day range for considering a patient to have the *H. pylori* infection eradicated at Week 8 was established to be ≥ Study Day 53. To consider a patient to still be infected with *H. pylori* at Week 8, a day range of ≥Study Day 29 was used if the patient was not considered to have *H. pylori* eradication at Week 8. Day 29 was chosen as the first day after the end of the study medication period. For the analysis of *H. pylori* eradication, if a patient had no available data or did not have the appropriate number of interpretable test results at Week 8 (within day range for that timepoint), the patient was included in the analysis of *H. pylori* eradication at that timepoint and was considered to be *H. pylori* positive at that timepoint.

RESULTS

The number of patients enrolled by each investigator is indicated in Table 5.

Table 5. Number of Patients Entered into Study by Investigator and Treatment (Study #126)

Site Number	Investigator	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid	Total
001	Barish	6	6	12
002	Kogut	10	10	20
003	Movva	0	1	1
004	DeAbate	6	4	10
005	Pyke	0	2	2
006	Martin	1	0	1
007	Shah	5	5	10
008	Māton	3	3	6
009	Kamyar	6	6	12
010	Caos	8	9	17
011	Lanza	6	6	12
012	Morris	0	0	0
013	Rosen	2	3	5
014	Wruble	3	4	7
015	Ballard	2	4	6
016	Kohagen	2	1	3
017	King	1	2	3
018	Fagel	2	1	3
019	Sloas	1	0	1
020	Hirschenbein	0	1	1
021	Berenson	0	1	1
022	Fennerty	0	0	0
023	Shaker	0	0	0
024	Fisher	0	0	0
025	Deering	0	0	0
026	Winkle	6	6	12
027	Winston	6	6	12
028	Gaddam	4	4	8
029	James	4	3	7
030	Ondrejicka	1	1	2
TOTAL		85	89	174

The number of patients who withdrew from the study are outlined in Table 6.

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TABLE 6
Patient Accounting
All Randomized Patients

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Study #126

Study Status	O 20 bid + A 1000 bid + C 500 bid n (%)	A 1000 bid + C 500 bid n (%)
Patients Enrolled	85	89
Completed the 8-Week Study Period	77 (91%)	76 (85%)
Discontinued from Study	8 (9%)	13 (15%)
Clinical Adverse Event	0 (0%)	2 (2%)
Laboratory Adverse Event	1 (1%)	0 (0%)
Lost to Follow-up	6 (7%)	8 (9%)
Patient Uncooperative	0 (0%)	1 (1%)
Other	1 (1%)	2 (2%)

NOTE: There were no significant differences observed between the treatment groups for proportion of patients who completed the study or for any reason discontinued from the study, ($p>0.050$), using Fisher's Exact Test.

Medical Officer's Comment: One of the two patients in the antibiotic only arm (patient ID 6046) who dropped out of the study due to "other", discontinued (H. pylori status at week 8 = no result) because of "no therapeutic response" at study day 23 and the other patient who dropped out of the study due to "other" (ID 6020) discontinued at study day 28 (H. pylori status at week 8 = infected) and the physician found a duodenal ulcer at study day 58. The one patient in the triple therapy arm who dropped out of the study due to a reason classified as "other" discontinued because the patient (ID number 6098) withdrew consent and did not have H. pylori assessed at the 8 week visit. The one patient who discontinued (patient ID 6154) due to a laboratory adverse event had elevated liver function tests (SGPT = 69 at end of therapy) that were possibly related to the study medications. The patient was on drug for 15 days and discontinued from the study on study day 92. No H. pylori eradication result was available for this patient.

The number of patients who were included (considered evaluable) or excluded (considered non-evaluable) from each analysis is summarized by treatment group in Table 7 according to the reason considered non-evaluable.

TABLE 7
Number of Patients Included and Excluded in the Statistical Analyses

Study #126

	O 20 bid + A 1000 bid + C 500 bid n (%)	A 1000 bid + C 500 bid n (%)
Total enrolled	85	89
Included in Efficacy Analysis		
"Intention-to-treat"	80 (94%)	84 (94%)
"Per-protocol"	68 (80%)	68 (76%)
Excluded from Efficacy Analysis		
"Intention-to-treat"	5 (6%)	5 (6%)
A. *H.pylori* not positive at baseline	4	5
B. No baseline DU	0	0
C. No study medication taken	2	0
"Per Protocol"	17 (20%)	21 (24%)
A. *H.pylori* not positive at baseline	4	5
B. Baseline DU not between 0.5 to 2.5 cm	0	0
C. Took antimicrobials, bismuth, or PPI prior to enrollment	1	2
D. Noncompliance of study medication	7	8
E. Concomitant antimicrobials or bismuth compounds	3	3
F. Concomitant H2-RA, PPI or sucralfate	1	1
G. No final endoscopy or efficacy measures taken	7	9
H. Other conditions/diseases	0	0
Included in Safety Analysis †	83 (98%)	89 (100%)

NOTE: A patient may be counted under more than one violation.

† Two patients in the O 20 bid + A 1000 bid + C 500 bid group (AN 6098, AN 6189) did not take any study medication and were not included in the analysis of safety data.

Table 8 lists each patient who was considered non-evaluable for either the "intention-to-treat" patient population or the "per-protocol" patient population and the reason(s) that each patient was considered non-evaluable for that analysis. Ten (10) of the 38 patients (26%) who were excluded from the "per-protocol" analysis were considered to be non-evaluable for the "per-protocol" patient population based on more than one criteria.

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TABLE 8
Patients Excluded from Efficacy Analysis
All Randomized Patients

APPEARS THIS WAY ON ORIGINAL

Study #126

Treatment Group	Site Number	AN	Excluded from ITT Analysis	Reason(s) for Exclusion †	Excluded from PP Analysis	Reason(s) for Exclusion †
O 20 bid + A 1000 bid + C 500 bid	001	6009	No		Yes	C
O 20 bid + A 1000 bid + C 500 bid	001	6219	No		Yes	E
O 20 bid + A 1000 bid + C 500 bid	002	6089	No		Yes	G
O 20 bid + A 1000 bid + C 500 bid	002	6128	No		Yes	E
O 20 bid + A 1000 bid + C 500 bid	002	6236	Yes	A	Yes	A
O 20 bid + A 1000 bid + C 500 bid	004	6026	Yes	A	Yes	A
O 20 bid + A 1000 bid + C 500 bid	008	6032	No		Yes	E
O 20 bid + A 1000 bid + C 500 bid	010	6098	Yes	A,C	Yes	A,D,G
O 20 bid + A 1000 bid + C 500 bid	011	6047	No		Yes	D,G
O 20 bid + A 1000 bid + C 500 bid	026	6206	No		Yes	G

† Descriptions of the reason(s) for exclusion are presented in the statistical/evaluability criteria section

TABLE 8 (cont.)
Patients Excluded from Efficacy Analysis
All Randomized Patients
Study #126

Treatment Group	Site Number	AN	Excluded from ITT Analysis	Reason(s) for Exclusion †	Excluded from PP Analysis	Reason(s) for Exclusion †
O 20 bid + A 1000 bid + C 500 bid	026	6209	No		Yes	D,G
O 20 bid + A 1000 bid + C 500 bid	026	6210	Yes	A	Yes	A,G
O 20 bid + A 1000 bid + C 500 bid	027	6184	No		Yes	D
O 20 bid + A 1000 bid + C 500 bid	027	6189	Yes	C	Yes	D,G
O 20 bid + A 1000 bid + C 500 bid	027	6190	No		Yes	D
O 20 bid + A 1000 bid + C 500 bid	028	6154	No		Yes	D
O 20 bid + A 1000 bid + C 500 bid	029	6180	No		Yes	F
A 1000 bid + C 500 bid	001	6010	No		Yes	E
A 1000 bid + C 500 bid	002	6090	No		Yes	D,G
A 1000 bid + C 500 bid	002	6233	No		Yes	E
A 1000 bid + C 500 bid	003	6001	Yes	A	Yes	A

† Descriptions of the reason(s) for exclusion are presented in the statistical/evaluability criteria section.

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ON ORIGINAL

TABLE 8 (cont.)
Patients Excluded from Efficacy Analysis
All Randomized Patients
Study #126

Treatment Group	Site Number	AN	Excluded from ITT Analysis	Reason(s) for Exclusion †	Excluded from PP Analysis	Reason(s) for Exclusion †
A 1000 bid + C 500 bid	004	6028	No		Yes	G
A 1000 bid + C 500 bid	004	6121	Yes	A	Yes	A
A 1000 bid + C 500 bid	008	6030	No		Yes	D,G
A 1000 bid + C 500 bid	009	6228	No		Yes	D,G
A 1000 bid + C 500 bid	010	6037	No		Yes	F
A 1000 bid + C 500 bid	010	6038	No		Yes	D
A 1000 bid + C 500 bid	011	6046	No		Yes	D
A 1000 bid + C 500 bid	011	6150	No		Yes	D
A 1000 bid + C 500 bid	011	6152	No		Yes	C,D,G
A 1000 bid + C 500 bid	015	6061	No		Yes	E
A 1000 bid + C 500 bid	015	6164	Yes	A	Yes	A
A 1000 bid + C 500 bid	026	6104	Yes	A	Yes	A,D,G
A 1000 bid + C 500 bid	026	6208	No		Yes	G
A 1000 bid + C 500 bid	026	6212	Yes	A	Yes	A
A 1000 bid + C 500 bid	027	6183	No		Yes	G
A 1000 bid + C 500 bid	029	6178	No		Yes	C
A 1000 bid + C 500 bid	029	6251	No		Yes	G

† Descriptions of the reason(s) for exclusion are presented in the statistical/evaluability criteria section

The results of the *H. pylori* status at Week 8 and results of the duodenal ulcer healed status by Week 8, as well as the day the patient discontinued from the study and reason for discontinuing from the study, are summarized in Table 9 for those patients considered non-evaluable for the "per-protocol" patient population.

TABLE 9

Listing of Results for Patients Excluded from "Per-Protocol" Analysis

Study #126

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H. pylori* Status at Week 8	Duodenal Ulcer Healed Status by Week 8
O 20 bid + A 1000 bid + C 500 bid	001	6009	58	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	001	6219	60	completed study	not infected	not healed
O 20 bid + A 1000 bid + C 500 bid	002	6089	55	lost to follow-up	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	002	6128	56	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	002	6236	64	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	004	6026	70	completed study	not infected	not healed
O 20 bid + A 1000 bid + C 500 bid	008	6032	56	completed study	not infected	not healed
O 20 bid + A 1000 bid + C 500 bid	010	6098	1	other reason (pt. withdrew consent)	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	011	6047	14	lost to follow-up	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	026	6206	29	lost to follow-up	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	026	6209	1	lost to follow-up	not evaluable	not available

TABLE 9 (cont.)

Listing of Results for Patients Excluded from "Per-Protocol" Analysis

Study #126

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H.pylori* Status at Week 8	Duodenal Ulcer Healed Status by Week 8
O 20 bid + A 1000 bid + C 500 bid	026	6210	29	lost to follow-up	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	027	6184	56	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	027	6189	1	lost to follow-up	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	027	6190	56	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	028	6154	92	lab AE	not evaluable	healed
O 20 bid + A 1000 bid + C 500 bid	029	6180	65	completed study	infected	healed
A 1000 bid + C 500 bid	001	6010	75	completed study	infected	healed
A 1000 bid + C 500 bid	002	6090	1	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	002	6233	56	completed study	infected	healed
A 1000 bid + C 500 bid	003	6001	58	completed study	not infected	healed
A 1000 bid + C 500 bid	004	6028	28	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	004	6121	54	completed study	not infected	healed
A 1000 bid + C 500 bid	008	6030	2	clinical AE	not evaluable	not available

TABLE 9 (cont.)

Listing of Results for Patients Excluded from "Per-Protocol" Analysis

Study #126

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H.pylori* Status at Week 8	Duodenal Ulcer Healed Status by Week 8
A 1000 bid + C 500 bid	009	6228	11	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	010	6037	56	completed study	not infected	healed
A 1000 bid + C 500 bid	010	6038	57	completed study	infected	not healed
A 1000 bid + C 500 bid	01H	6046	23	other reason (no therapeutic response)	not evaluable	not available
A 1000 bid + C 500 bid	011	6150	47	patient uncooperative	infected	not healed
A 1000 bid + C 500 bid	011	6152	1	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	015	6061	77	completed study	infected	not healed
A 1000 bid + C 500 bid	015	6164	64	completed study	not infected	not healed
A 1000 bid + C 500 bid	026	6104	1	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	026	6208	31	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	026	6212	57	completed study	infected	not healed
A 1000 bid + C 500 bid	027	6183	42	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	029	6178	55	completed study	not infected	healed
A 1000 bid + C 500 bid	029	6251	40	lost to follow-up	not evaluable	not available

Table 10 presents the same results for those patients considered non-evaluable for the "intention-to-treat" patient population

TABLE 10
Listing of Results for Patients Excluded from "Intention-to-Treat" Analysis
Study #126

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H. pylori* Status at Week 8	Duodenal Ulcer Healed Status by Week 8
O 20 bid + A 1000 bid + C 500 bid	002	6236	64	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	004	6026	70	completed study	not infected	not healed
O 20 bid + A 1000 bid + C 500 bid	010	6098	1	other reason (pt. withdrew consent)	infected†	not healed‡
O 20 bid + A 1000 bid + C 500 bid	026	6210	29	lost to follow-up	infected†	not healed‡
O 20 bid + A 1000 bid + C 500 bid	027	6189	1	lost to follow-up	infected†	not healed‡
A 1000 bid + C 500 bid	003	6001	58	completed study	not infected	healed
A 1000 bid + C 500 bid	004	6121	54	completed study	not infected	healed
A 1000 bid + C 500 bid	015	6164	64	completed study	not infected	not healed
A 1000 bid + C 500 bid	026	6104	1	lost to follow-up	infected†	not healed‡
A 1000 bid + C 500 bid	026	6212	57	completed study	infected	not healed

† *H. pylori* status at Week 8 was not evaluable, but was estimated as infected for the "intention-to-treat" analysis.

‡ Duodenal ulcer healed status was not available, but was estimated as not healed for the "intention-to-treat" analysis.

DEMOGRAPHIC RESULTS

There was no significant difference in demographic characteristics for either the per-protocol or the intent-to-treat populations. This includes gender, age, race, ulcer size, global ulcer symptoms, smoking status, and alcohol use.

COMPLIANCE RESULTS

There was no difference in study medication compliance between treatment groups. The percent of patients that were compliant with study medication is outlined in Table 11.

TABLE 11
Patient Compliance of Study Medication Taken
All Randomized Patients
Study #126

APPEARS THIS WAY ON ORIGINAL

	O 20 bid + A 1000 bid + C 500 bid (N = 85)	A 1000 bid + C 500 bid (N = 89)
Number (%) of Patients	n (%)	n (%)
Compliant	78 (92%)	81 (91%)
Noncompliant	7 (8%)	8 (9%)

NOTE: There was no significant difference observed between the treatment groups, ($p>0.050$), using Fisher's Exact Test.

EFFICACY RESULTS

The sponsor's Per-protocol and Intent-to-Treat eradication rates and 95% confidence intervals are presented in Table 12.

TABLE 12
***H. pylori* Eradication at Week 8**
[95% Confidence Intervals]
Per-Protocol Analysis and Intent-to-Treat Analysis
Study #126

	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid
H. pylori Eradicated	n/N (%)	n/N (%)
Week 8 Per-Protocol	49/63 (78%)* [68%, 88%]	29/65 (45%) [33%, 57%]
Week 8 Intent-to-Treat	55/80 (69%)* [59%, 79%]	31/84 (37%) [27%, 47%]

* Significantly different from A 1000 bid + C 500 bid, ($p<0.001$), using a logistic regression model.

Medical Officer Comments: Two patients discontinued from the study because of a clinical Adverse Event. Only one of these patients (ID #6030) discontinued because of an adverse event that was thought to be related to the study medication. Information on the two patients who discontinued due to a clinical AE are shown below:

PATID	ACTION TAKEN	A E	CAUSE	INTEN
6105	None	DYSPEPSIA -	unlikely	Moderate
6030	Test Drug	NERVOUSNESS	Probably Related	Moderate
6030	Test Drug	ANXIETY	Probably Related	Moderate

One patient (ID # 6020) discontinued the study because the physician found a duodenal ulcer following treatment that required treatment and another patient (ID # 6046) discontinued because there was no therapeutic response. Patient 6154 (triple therapy) withdrew at study day 15 due to an adverse event that was possibly related to the study medication (elevated LFTs) and patient 6098 (triple therapy) withdrew consent on the first study day.

Three patients were considered "non-evaluable" in the per-protocol analysis (6154, 6030, and 6046). These patients might be best classified as "evaluable failures. If so, the eradication rate would be 43% (29/67) and 76.5% (49/64) for the dual therapy and triple therapy regimen, respectively.

Eradication rates by demographic characteristics are presented in Table 13. Numeric differences were seen for many of these characteristics. For example, males had lower eradication rates than females, blacks had lower eradication rates than Caucasians, and smokers had lower eradication rates as compared with non-smokers.

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ON ORIGINAL

TABLE 13
***H. pylori* Eradication at Week 8 - Subgroup Analysis**
Number (%) of Patients
Per-Protocol Analysis (Study #126)

	O 20 bid + A 1000 bid + C 500 bid		A 1000 bid + C 500 bid	
	n/N (%)		n/N (%)	
Overall Eradication Rates	49/63	(78%)	29/65	(45%)
Gender				
Males	29/40	(73%)	21/50	(42%)
Females	20/23	(87%)	8/15	(53%)
Race				
Caucasian	39/49	(80%)	22/46	(48%)
Black	8/12	(67%)	7/19	(37%)
Other	2/2	(100%)	0/0	---
Age				
≤65 years	44/58	(76%)	27/58	(47%)
>65 years	5/5	(100%)	2/7	(29%)
Baseline Smoking Status				
Smokers	19/27	(70%)	12/31	(39%)
Non-Smokers	30/36	(83%)	17/34	(50%)
Largest Baseline Duodenal Ulcer Size				
≤1 cm	43/54	(80%)	23/55	(42%)
>1 cm	6/9	(67%)	6/10	(60%)

NOTE: No statistical comparisons were made between the treatment groups for any of the demographic subgroups.

TABLE 14
Comparison of *H. pylori* Diagnostic Methods
All Patients With Interpretable Test Results
Both Treatment Groups Combined (Study #126)

	Baseline			Week 8		
CLOtest® vs. Histology						
	Histology results			Histology results		
CLOtest® results	Positive	Negative	Total	Positive	Negative	Total
Positive	162	8	170	40	0	40
Negative	0	0	0	13	92	105
Total	162	8	170	53	92	145
McNemar's Test p-value:	not calculated			p <0.001*		
Kappa statistic: 95% CI:	not calculated			κ = 0.80 (0.69, 0.90)		
CLOtest® vs. Culture						
	Culture results			Culture results		
CLOtest® results	Positive	Negative	Total	Positive	Negative	Total
Positive	144	21	165	36	4	40
Negative	0	0	0	11	85	96
Total	144	21	165	47	89	136
McNemar's Test p-value:	not calculated			p = 0.119		
Kappa statistic: 95% CI:	not calculated			κ = 0.75 (0.63, 0.87)		
Histology vs. Culture						
	Culture results			Culture results		
Histology results	Positive	Negative	Total	Positive	Negative	Total
Positive	141	14	155	43	8	51
Negative	1	7	8	2	80	82
Total	142	21	163	45	88	133
McNemar's Test p-value:	p = 0.001*			p = 0.109		
Kappa statistic: 95% CI:	κ = 0.44 (0.22 ,0.67)			κ = 0.84 (0.74, 0.93)		

* The proportion of patients with positive test results is significantly different between the two diagnostic tests, ($p \leq 0.050$), using McNemar's test.

Medical Officer's Comment: The false negative rate of CLOtest as compared to culture is 11/47 (23%) at the F/U visit. This is similar to the false negative rate of the CLOtest as compare to histology (13/53, 24%).

Statistical Reviewer's Comment: The kappa statistics suggest that there is a fair amount of agreement between the various pairs of tests at Week 8. The results from McNemar's test, however, suggest that the proportion of patients with a positive test at Week 8 is different for CLOtest vs. histology.

The distribution of tests results at baseline and week 8 is presented in Table 15 and 16.

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TABLE 15
Classification of *H. pylori* Infection, Evaluability, and Eradication Based on Endoscopic Tests for *H. pylori* at Baseline All Randomized Patients Study #126

Pre-therapy (Baseline) Diagnosis					
Culture	Histology	CLOtest® †	Patient Status	O 20 bid + A 1000 bid + C 500 bid (N = 85)	A 1000 bid + C 500 bid (N = 89)
Three tests available					
+	+	+	Infected	67	74
+	+	-	Infected	—	—
+	-	+	Infected	0	1
+	-	-	Infected	—	—
-	+	+	Infected	6	8
-	-	+	Not infected	3	4
-	+	-	Not infected	—	—
-	-	-	Not infected	—	—
Two tests available					
+	+	N/A	Infected	—	—
+	-	N/A	Infected	—	—
-	+	N/A	Not evaluable	—	—
-	-	N/A	Not infected	—	—
+	N/A	+	Infected	1	1
+	N/A	-	Infected	—	—
-	NA	+	Not evaluable	0	0
-	NA	-	Not infected	—	—
N/A	+	+	Infected	7	0
N/A	+	-	Not evaluable	—	—
N/A	-	+	Not evaluable	0	0
N/A	-	-	Not infected	—	—
One test available					
+	N/A	N/A	Infected	—	—
-	N/A	N/A	Not evaluable	—	—
N/A	N/A	+	Not evaluable	1	1
N/A	N/A	-	Not evaluable	—	—
N/A	+	N/A	Not evaluable	—	—
N/A	-	N/A	Not evaluable	—	—

† Patient must have positive CLOtest® to receive study medication and to be included in the study.

TABLE 16
Classification of *H. pylori* Infection, Evaluability, and Eradication Based on Endoscopic Tests for *H. pylori* at Week 8 All Randomized Patients

Study #126

Post-therapy (Week 8) Diagnosis					
Culture	Histology	CLOtest®	Patient Status	O 20 bid + A 1000 bid +C 500 bid (N = 85)	A 1000 bid + C 500 bid (N = 89)
Three tests available					
+	+	+	Infected	5	30
+	+	-	Infected	4	4
+	-	+	Infected	0	0
+	-	-	Infected	0	2
-	+	+	Infected	1	3
-	-	+	Infected	0	0
-	+	-	Infected	2	2
-	-	-	Eradicated	50	30
Two tests available					
+	+	N/A	Infected	0	0
+	-	N/A	Infected	0	0
-	+	N/A	Infected	0	0
-	-	N/A	Eradicated	0	0
+	N/A	+	Infected	0	1
+	N/A	-	Infected	1	0
-	NA	+	Infected	0	0
-	NA	-	Eradicated	1	0
N/A	+	+	Infected	1	0
N/A	+	-	Infected	1	0
N/A	-	+	Infected	0	0
N/A	-	-	Eradicated	6	4
One test available					
+	N/A	N/A	Infected	0	0
-	N/A	N/A	Not evaluable	0	0
N/A	N/A	+	Infected	0	0
N/A	N/A	-	Not evaluable	2	1
N/A	+	N/A	Infected	0	0
N/A	-	N/A	Not evaluable	0	0
Zero tests available					
N/A	N/A	N/A	Not evaluable	11	12

Ulcer healing rates at week 8 are presented in Table 17 for the per-protocol analysis.

TABLE 17
Duodenal Ulcer Healed Status by Week 8
Per-Protocol and Intent-to-Treat Analyses

Study #126

Per-Protocol	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid
Duodenal Ulcer Healed	n/N (%)	n/N (%)
by Week 8	56/68 (82%)	49/68 (72%)

Intent-to-Treat	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid
Duodenal Ulcer Healed	n/N (%)	n/N (%)
by Week 8	62/80 (78%)	53/84 (63%)

NOTE: There was no significant difference between the treatment groups, using a logistic regression model (Per-protocol, p= 0.166, ITT, p= 0.057)

The relationship between *H. pylori* eradication and ulcer healing is shown in Table 18 for each treatment group and both treatments combined. For both treatment groups combined who were considered to have *H. pylori* eradication at Week 8, 85% of the patients (66 of 78 patients) had a healed duodenal ulcer by Week 8. Of the patients who were not considered to have *H. pylori* eradication at Week 8, only 62% of the patients (31 of 50 patients) had a healed duodenal ulcer by Week 8. For the O 20 bid + A 1000 bid + C 500 bid group, there was no significant association observed between *H. pylori* eradication status and duodenal ulcer healed status. There was a significant association between *H. pylori* eradication status and duodenal ulcer healed status for the A 1000 bid + C 500 bid group. Of the patients who were considered to have *H. pylori* eradication at Week 8, 86% of the patients (25 of 29 patients) had a healed duodenal ulcer by Week 8. Of the patients not considered to have *H. pylori* eradication by Week 8, only 58% of the patients (21 of 36 patients) had a healed duodenal ulcer by Week 8.

TABLE 18
Duodenal Ulcer Healed Status by Week 8 vs. *H. pylori* Eradication Status at Week 8
Number of Patients
Per-Protocol Analysis

Study #126

	O 20 bid + A 1000 bid + C 500 bid			A 1000 bid + C 500 bid			Both treatment groups combined		
	Duodenal Ulcer Healed by Week 8								
H.pylori Eradicated at Week 8	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	41	8	49	25	4	29	66	12	78
No	10	4	14	21	15	36	31	19	50
Total	51	12	63	46	19	65	97	31	128
Fisher's Exact Test p-value:	p = 0.440			p = 0.027 *			p < 0.001 *		

* There was significant association observed between *H. pylori* eradication at Week 8 and duodenal ulcer healed status by Week 8, ($p \leq 0.050$), using Fisher's Exact Test.

The time to ulcer-free status is presented in Table 19 and Figure 2. There was no significant difference in the time-to-event curves for the time until patient is free of ulcer symptoms between the O 20 bid + A 1000 bid + C 500 bid group and A 1000 bid + C 500 bid group. However, the median time until patients were free of ulcer symptoms was 15 days for the patients in the O 20 bid + A 1000 bid + C 500 bid treatment group and 23 days for the patients in the A 1000 bid + C 500 bid treatment group indicating a trend in favor of the O 20 bid + A 1000 bid + C 500 bid group.

TABLE 19
Time Until Patient Is Free of Ulcer Symptoms (in Days)
Per-Protocol Analysis

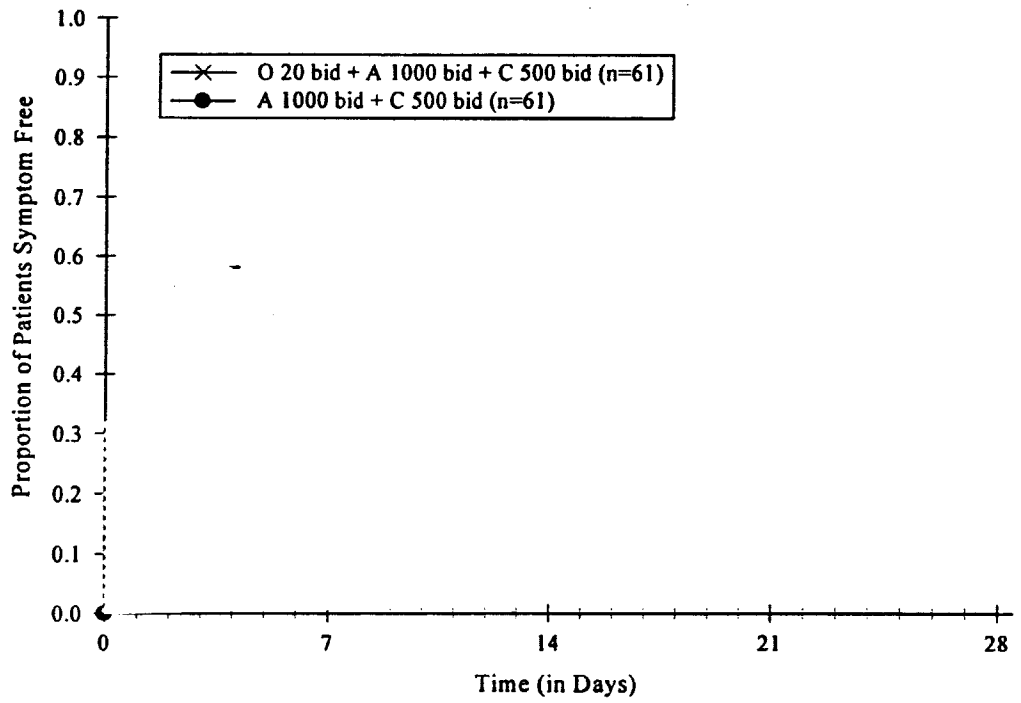
Study #126

Percentiles	O 20 bid +A 1000 bid + C 500 bid (N = 61)	A 1000 bid +C 500 bid (N = 61)
25th %	5 days	10 days
50th % (Median)	15 days	23 days
75th %	26 days	28 days

NOTE: There was no significant difference between the time-to-event curves for O 20 bid + A 1000 bid + C 500 bid vs. A 1000 bid + C 500 bid, (p=0.089), using Cox's proportional hazards regression model.

FIGURE 2
TIME UNTIL PATIENT IS FREE OF ULCER SYMPTOMS
PER-PROTOCOL ANALYSIS

STUDY #126



The average GELUSIL usage is shown in Table 20. Mean usage was less than 1 tablet per day.

TABLE 20
Average GELUSIL® Usage (in tablets per day) - Days 1 through 28
Per-Protocol Analysis

Study #126

Treatment Group	N	Mean	SD	Range
O 20 bid + A 1000 bid + C 500 bid	66	0.38	0.72	0 to 3.6
A 1000 bid + C 500 bid	68	0.72	1.01	0 to 4.3

NOTE: No statistical comparisons were made between treatment groups.

SAFETY ANALYSES

The number of clinical adverse event and laboratory adverse events are summarized in Table 21 and 22, respectively.

TABLE 21
Clinical Adverse Events Summary
Number (%) of Patients
Weeks 1 through 8
All Randomized Patients Who Took At Least One Dose of Study Medication

Study #126

-	O 20 bid + A 1000 bid + C 500 bid (N = 83)	A 1000 bid + C 500 bid (N = 89)
Number (%) of Patients:	n (%)	n (%)
With ≥ 1 clinical adverse event	39 (47%)	46 (52%)
With a possibly or probably drug related clinical adverse event	18 (22%)	27 (30%)
With a serious clinical adverse event	0 (0%)	0 (0%)
Discontinued due to a clinical adverse event	0 (0%)	2 (2%)

NOTE: There were no significant differences observed between the treatment groups, ($p>0.050$), using a Fisher's Exact Test.

TABLE 21
Laboratory Adverse Events Summary
Number (%) of Patients
Weeks 1 through 8
All Randomized Patients Who Took At Least One Dose of Study Medication†

Study #126

	O 20 bid + A 1000 bid + C 500 bid (N = 82) †	A 1000 bid + C 500 bid (N = 85) †
Number (%) of Patients:	n (%)	n (%)
With ≥ 1 laboratory adverse event	5 (6%)	6 (7%)
With possibly or probably drug related laboratory adverse event	4 (5%)	3 (4%)
Serious laboratory adverse event	0 (0%)	0 (0%)
Discontinued due to laboratory adverse event	1 (1%)	0 (0%)

† Number of patients who took at least one dose of study medication and who had any laboratory tests performed after baseline.

NOTE: There were no significant differences observed between the treatment groups, ($p>0.050$), using a Fisher's Exact Test.

REVIEWERS' CONCLUSIONS OF STUDY 126

This was a well conducted, randomized, clinical trial which convincingly demonstrated the superiority of triple therapy (O + A + C) over antibiotics alone (A + C) when given for 10 days with twice daily dosing. The lower bound of the 95% confidence interval of the point estimate for triple therapy using the ITT analysis was 59% slightly less than the 60 percent threshold as suggested by the Division.

In addition, multiple interesting observations were made:

- *The eradication rate among smokers was lower for both arms regardless of treatment as compared with non-smokers (this difference was not statistically significant).*

- *The false negative rate of CLOtest at the follow-up visit as compared with culture (alone) and histology (alone) was quite high (23% and 24%, respectively). This casts doubt on the utility of the CLOtest to monitor the effectiveness of treatment.*
- *There was no significant difference in ulcer incidence rates at 4 weeks post-treatment between the triple therapy and antibiotic alone arms (82% versus 72%, per-protocol; 78% versus 63%, intent-to-treat). This suggests that antibiotics alone may be sufficient to achieve adequate ulcer healing at 4 weeks post-treatment.*
- *H. pylori eradication was associated with an improved ulcer healing rate at the 4-week follow-up visit (85%) as compared with the healing rate among patients who were not eradicated of H. pylori (62%) when combining treatment groups.*
- *Although the median time to resolution in ulcer symptoms was less in the triple therapy arm (15 days) as compared with antibiotics alone (23 days), there was no difference between treatment groups in the time until symptom free curves. Although there was less than 1 tablet of Gelusil used per day, the mean Gelusil usage for antibiotic only therapy was about twice that of triple therapy.*
- *The proportion of patients with adverse events (and related adverse events) were similar between treatments.*

MEDICAL AND STATISTICAL REVIEW OF STUDY 127

INVESTIGATORS

Thirty four (34) primary investigators participated in the trial. This study used identical contract organizations and central laboratories to those used in study 126.

TABLE 22
List of Investigators (Study #127)

Primary Investigator	Site #	Facility	Location
Paul J. Ballinger, M.D.	30	Department Wenatchee Valley Clinic	820 N. Chelan Wenatchee, WA 98801
Thomas Bianchi, M.D.	023	Community Medical Center	875 Friendship Road Tallassee, AL 36078
Philip Bird, MD.	05	Research Associates of Norman, Inc.	1125 North Porter Suite 302 Norman, OK 73071
Milan Brandon, MD	01	California Research Foundation	2800 Third Avenue San Diego, CA 92103-6281
Stuart Chen, MD	34	Truman Medical Center	2301 Holmes Street Kansas City, MO 64108
Marta Ligia Davila, MD	19	Palo Alto VAMC (111 GI)	3801 Miranda Avenue Palo Alto, CA 94304
Carolyn Diamant, MD	17	Specialty Medical Clinics	3737 Moraga Avenue Suite A305 San Diego, CA 92117
Michael S. Epstein, MD	14	Private Practice	621 Ridgely Avenue Suite 201 Annapolis, MD 21401
Atilla Ertan, MD	02	Baylor College of Medicine	6550 Fannin SM 1122 Houston, TX 77030
Duane D. Fitch, MD,FACP	10	Triangle East Gastroenterology, PA	1704 South Tarboro Street P.O. Box 3526 Wilson, NC 27895-3526
Stuart A. Frank MD,PC	04	Diseases of the Digestive System	1720 Gunbarrel Road Suite 206 Chattanooga, TN 37421
Hans Fromm, MD	09	University Hospital Office	G323 901 23rd Street N.W. Washington DC 20037
John Goff, MD	32	Private Practice	8850 Ralston Road Arvada, CO 80002
Martin, I Golding, MD	35	Montgomery Gastroenterology, PA	12012 Veirs Mills Road Wheaton, MD 20906
R. Bruce Johnson, MD	12	Sharp Rees-Stealy Medical Group	2001 Fourth Avenue San Diego, CA 92101

TABLE 22 (cont.)
List of Investigators
Study #127

Primary Investigator	Site #	Facility	Location
Robert R. Johnson, MD	25	Private Practice	877 South Avernon Way Suite 201 Tucson, AZ 85711
Deryck Joseph, MD	08	Private Practice	833 Princeton Avenue, S.W. Birmingham, AL 35211
David Kogut, MD	36	Piedmont Gastroenterology	1835 Davie Avenue Statesville, NC 28677
Richard Krause, MD	22	Parkridge Medical Center	2337 McCallie Avenue Plaza One, Suite 400 Chattanooga, TN 37404
Michael D. Kurtz, MD	28	Private Practice	3923 Waring Road Suite A Oceanside, CA 92056
Joel Levine, MD	31	University of Colorado Health Sciences Center	4200 East 9th Ave. B158 Denver, CO 80262
Antoinette Mangione, MD	33	Hill-Top Research Inc.	Einstein Center One 9880 Bustleton Ave, Suite 203 Philadelphia, PA 19115
James Mertesdorf, MD	16	Hanover Medical Specialists, PA	1515 Doctor's Circle Wilmington, NC 28401
David A. Peura, MD	20	University of Virginia Health Science Center	Division of Gastroenterology Box 145 Charlottesville, VA 22903
Harvey Resnick, MD	24	R/D Clinical Research Inc.	135 Oyster Creek Drive Suite W Lake Jackson, TX 77566
Michele Reynolds, MD	29	Hill-Top Research Inc.	8305 Walnut Hill Lane Dallas, TX 75231
Dennis S. Riff, MD	11	A.G.M.G. Research	1211 West La Palma Ave. Suite 306 Anaheim, CA 92801
Peter Ripley, MD	06	Clinical Studies	23 H Whitis Path South Yarmouth, MA 02664
Herbert Rubin, MD	03	Private Practice	465 North Roxbury Drive Suite 711 Beverly Hills, CA 90210

TABLE 22 (cont.)
List of Investigators
Study #127

Primary Investigator	Site #	Facility	Location
Michael A. Safdi, MD	13	Consultants for Clinical Research	2925 Vernon Place Suite 100 Cincinnati, OH 45219
David Silvers, MD	15	Private Practice	4720 South I-10 Service Rd. #501 Metairie, LA 70001
Raymond E. Tidman, MD	27	Mountain Medical	101 Burns Professional Bldg. Blue Ridge, GA 30513
Gary W. Varilek, MD	18	University of Kentucky	800 Rose Street Room 634 Lexington, KY 40536
Z. Reno Vlahcevic, MD	21	McGuire D.V.A.M.C.	Gastroenterology Section (111N) 1201 Broad Rock Road Richmond, VA 23249

Statistical Reviewer's Comment: Several of the investigators for this trial were also involved in Abbott study 56268 (e.g., Drs. Kogut, Peura, and Rubin). It is unclear whether any patients enrolled in this study by these investigators were also enrolled at a different timepoint in the Abbott study.

Whenever there is overlap of investigators between studies, one questions whether the trials can be deemed independent as we would like them to be (see similar note in study 126). However, there is no overlap of investigators between studies 126 and 127, so we do have two independent trials of this therapy for this indication.

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OBJECTIVES AND STUDY DESIGN

The study objectives and study design for study 127 were identical to study 126.

RESULTS

The number of patients enrolled by each investigator is shown in Table 23.

TABLE 23
Number of Patients Entered into Study 127 by Investigator and Treatment Group

Site Number	Investigator	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid	Total
001	Brandon	4	4	8
002	Ertan	4	4	8
003	Rubin	5	6	11
004	Frank	1	0	1
005	Bird	7	7	14
006	Ripley	0	1	1
007	not initiated	---	---	---
008	Joseph	0	0	0
009	Fromm	2	2	4
010	Fitch	9	9	18
011	Riff	9	10	19
012	Johnson, B.	4	4	8
013	Safdi	4	3	7
014	Epstein	1	0	1
015	Silvers	4	4	8
016	Mertesdorf	1	1	2
017	Diament	1	2	3
018	Varilek	4	4	8
019	Davila	0	0	0
020	Peura	0	1	1
021	Vlahcevic	2	2	4
022	Krause	5	4	9
023	Bianchi	2	2	4
024	Resnick	4	2	6
025	Johnson, R.	0	0	0
026	not initiated	---	---	---

TABLE 23 (cont.)
Number of Patients Entered into Study by Investigator and Treatment Group

Study #127

Site Number	Investigator	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid	Total
027	Tidman	2	3	5
028	Kurtz	1	0	1
029	Reynolds	1	0	1
030	Ballinger	2	0	2
031	Levine	0	0	0
032	Goff	2	3	5
033	Mangione	0	1	1
034	Chen	5	5	10
035	Golding	0	0	0
036	Kogut	0	1	1
TOTAL		86	85	171

The number of patients who withdrew from the study are outlined in Table 24.

TABLE 24
Patient Accounting, All Randomized Patients (Study #127)

Study Status	O 20 bid + A 1000 bid + C 500 bid n (%)	A 1000 bid + C 500 bid n (%)
Patients Enrolled	86	85
Completed the 8 Week Study Period	77 (90%)	76 (89%)
Discontinued from Study	9 (10%)	9 (11%)
Clinical Adverse Event	4 (5%)	4 (5%)
Lost to Follow-up	0 (0%)	1 (1%)
Deviation from Protocol	4 (5%)	0 (0%)
Patient Uncooperative	1 (1%)	0 (0%)
Other	0 (0%)	4 (5%)

Note: There were no significant differences observed between the treatment groups for proportion of patients who completed the study or for any reason discontinued from the study, ($p>0.050$), using Fisher's Exact Test.

TABLE 25, Number of Patients Included and Excluded in the Statistical Analyses
Study #127

	O 20 bid + A 1000 bid + C 500 bid n (%)	A 1000 bid + C 500 bid n (%)
Total enrolled	86	85
Included in Efficacy Analysis		
"Intention-to-treat"	77 (90%)	83 (98%)
"Per-protocol"	66 (77%)	67 (79%)
Excluded from Efficacy Analysis		
"Intention-to-treat"	9 (10%)	2 (2%)
A. *H.pylori* not positive at baseline	8	2
B. No baseline DU	0	0
C. No study medication taken	1	0
"Per Protocol"	20 (23%)	18 (21%)
A. *H.pylori* not positive at baseline	8	2
B. Baseline DU not between 0.5 to 2.5 cm	0	1
C. Took antimicrobials, bismuth, or PPI prior to enrollment	3	0
D. Noncompliance of study medication	11	5
E. Concomitant antimicrobials or bismuth compounds	2	7
F. Concomitant H2-RA, PPI or sucralfate	1	0
G. No final endoscopy or efficacy measures taken	8	8
H. Other conditions/diseases	0	1
I. Patient also in Study #126	0	0
Included in Safety Analysis†	85 (99%)	85 (100%)

Note: A patient may be counted under more than 1 violation.

† One patient in the O 20 bid + A 1000 bid + C 500 bid group (AN 6601) did not take any study medication and was not included in the analysis of safety data.

Statistical Reviewer's Comment: The number of patients included in the intent-to-treat analysis was lower for triple therapy patients (this difference was marginally statistically significant, p=0.06 using Fisher's exact test). The difference in rates is mostly due to the greater number of triple therapy patients excluded for H. pylori negative status at baseline.

A larger number of triple therapy patients were noncompliant with study medication, 11 versus 5. A larger number of antibiotic alone therapy patients took concomitant antimicrobials or bismuth compounds, 7 versus 2.

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Table 26 lists each patient who was considered non-evaluable for either the "intention-to-treat" patient population or the "per-protocol" patient population and the reason(s) that each patient was considered non-evaluable for that analysis.

TABLE 26
Patients Excluded from Efficacy Analysis
All Randomized Patients (Study #127)

Treatment Group	Site Number	AN	Excluded from ITT Analysis	Reason(s) for Exclusion †	Excluded from PP Analysis	Reason(s) for Exclusion †
O 20 bid + A 1000 bid + C 500 bid	3	6520	No		Yes	C
O 20 bid + A 1000 bid + C 500 bid	3	6607	Yes	A	Yes	A
O 20 bid + A 1000 bid + C 500 bid	3	6608	No		Yes	D,E
O 20 bid + A 1000 bid + C 500 bid	4	6516	Yes	A	Yes	A,D,G
O 20 bid + A 1000 bid + C 500 bid	5	6586	Yes	A	Yes	A,D,G
O 20 bid + A 1000 bid + C 500 bid	5	6666	No		Yes	C
O 20 bid + A 1000 bid + C 500 bid	12	6676	Yes	A	Yes	A,D,G
O 20 bid + A 1000 bid + C 500 bid	13	6526	No		Yes	E
O 20 bid + A 1000 bid + C 500 bid	13	6642	No		Yes	D,G
O 20 bid + A 1000 bid + C 500 bid	15	6714	No		Yes	D,G
O 20 bid + A 1000 bid + C 500 bid	17	6556	Yes	A	Yes	A

† Descriptions of the reason(s) for exclusion are presented in the protocol description for study 126

TABLE 26 (cont.)
Patients Excluded from Efficacy Analysis
All Randomized Patients

Study #127

Treatment Group	Site Number	AN	Excluded from ITT Analysis	Reason(s) for Exclusion †	Excluded from PP Analysis	Reason(s) for Exclusion †
O 20 bid + A 1000 bid + C 500 bid	21	6626	No		Yes	D
O 20 bid + A 1000 bid + C 500 bid	22	6557	No		Yes	C
O 20 bid + A 1000 bid + C 500 bid	22	6623	No		Yes	D,F
O 20 bid + A 1000 bid + C 500 bid	22	6645	Yes	A	Yes	A
O 20 bid + A 1000 bid + C 500 bid	23	6564	No		Yes	D,G
O 20 bid + A 1000 bid + C 500 bid	24	6592	No		Yes	D,G
O 20 bid + A 1000 bid + C 500 bid	27	6597	Yes	A	Yes	A
O 20 bid + A 1000 bid + C 500 bid	27	6600	Yes	A	Yes	A
O 20 bid + A 1000 bid + C 500 bid	28	6601	Yes	C	Yes	D,G
A 1000 bid + C 500 bid	2	6573	No		Yes	D,G
A 1000 bid + C 500 bid	2	6576	No		Yes	G
A 1000 bid + C 500 bid	11	6567	No		Yes	E

† Descriptions of the reason(s) for exclusion are presented in the protocol for study 126

TABLE 26 (cont.)
Patients Excluded from Efficacy Analysis
All Randomized Patients

Study #127

Treatment Group	Site Number	AN	Excluded from ITT Analysis	Reason(s) for Exclusion †	Excluded from PP Analysis	Reason(s) for Exclusion †
A 1000 bid + C 500 bid	12	6539	No		Yes	B
A 1000 bid + C 500 bid	12	6540	No		Yes	E
A 1000 bid + C 500 bid	13	6644	No		Yes	E,G
A 1000 bid + C 500 bid	15	6713	No		Yes	E
A 1000 bid + C 500 bid	16	6548	No		Yes	E
A 1000 bid + C 500 bid	17	6553	No		Yes	D,G
A 1000 bid + C 500 bid	18	6749	No		Yes	E
A 1000 bid + C 500 bid	22	6621	No		Yes	E
A 1000 bid + C 500 bid	24	6590	Yes	A	Yes	A
A 1000 bid + C 500 bid	24	6591	No		Yes	D,G
A 1000 bid + C 500 bid	27	6598	No		Yes	H
A 1000 bid + C 500 bid	27	6599	No		Yes	G
A 1000 bid + C 500 bid	33	6689	Yes	A	Yes	A
A 1000 bid + C 500 bid	34	6693	No		Yes	D,G
A 1000 bid + C 500 bid	34	6736	No		Yes	D,G

† Descriptions of the reason(s) for exclusion are presented in the protocol for study 126

The results of the *H. pylori* status at Week 8 and results of the duodenal ulcer healed status by Week 8, as well as the day the patient discontinued from the study and reason for discontinuing from the study, are summarized in Table 27 for those patients considered non-evaluable for the "per-protocol" patient population.

TABLE 27

Listing of Results for Patients Excluded from "Per-Protocol" Analysis (Study #127)

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H. pylori* Status at Week 8	DU Healed Status by Week 8
O 20 bid + A 1000 bid + C 500 bid	3	6520	74	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	3	6607	74	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	3	6608	55	completed study	not infected	not healed
O 20 bid + A 1000 bid + C 500 bid	4	6516	60	deviation from protocol	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	5	6586	23	deviation from protocol	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	5	6666	59	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	12	6676	7	deviation from protocol	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	13	6526	56	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	13	6642	4	clinical AE	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	15	6714	7	clinical AE	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	17	6556	58	completed study	not infected	not healed
O 20 bid + A 1000 bid + C 500 bid	21	6626	58	completed study	infected	healed

TABLE 27 (cont.)
Listing of Results for Patients Excluded from "Per-Protocol" Analysis
Study #127

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H. pylori* Status at Week 8	Duodenal Ulcer Healed Status by Week 8
O 20 bid + A 1000 bid + C 500 bid	22	6557	56	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	22	6623	64	clinical AE	infected	not healed
O 20 bid + A 1000 bid + C 500 bid	22	6645	62	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	23	6564	20	patient uncooperative	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	24	6592	16	clinical AE	not evaluable	not available
O 20 bid + A 1000 bid + C 500 bid	27	6597	54	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	27	6600	54	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	28	6601	-1	deviation from protocol	not evaluable	not available
A 1000 bid + C 500 bid	2	6573	25	other reason (pt. withdrew consent)	not evaluable	not available
A 1000 bid + C 500 bid	2	6576	50	other reason (pt. withdrew consent)	not evaluable	not available
A 1000 bid + C 500 bid	11	6567	60	completed study	infected	healed
A 1000 bid + C 500 bid	12	6539	53	completed study	infected	not healed
A 1000 bid + C 500 bid	12	6540	60	completed study	infected	healed

TABLE 27 (cont.)
Listing of Results for Patients Excluded from "Per-Protocol" Analysis

Study #127

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H.pylori* Status at Week 8	Duodenal Ulcer Healed Status by Week 8
A 1000 bid + C 500 bid	13	6644	49	clinical AE	not evaluable	not available
A 1000 bid + C 500 bid	15	6713	55	completed study	not infected	healed
A 1000 bid + C 500 bid	16	6548	61	completed study	infected	not healed
A 1000 bid + C 500 bid	17	6553	11	clinical AE	not evaluable	not available
A 1000 bid + C 500 bid	18	6749	56	completed study	infected	healed
A 1000 bid + C 500 bid	22	6621	59	completed study	infected	not healed
A 1000 bid + C 500 bid	24	6590	57	completed study	not infected	healed
A 1000 bid + C 500 bid	24	6591	11	clinical AE	not evaluable	not available
A 1000 bid + C 500 bid	27	6598	56	completed study	not infected	not healed
A 1000 bid + C 500 bid	27	6599	29	lost to follow-up	not evaluable	not available
A 1000 bid + C 500 bid	33	6689	118	completed study	not infected	healed
A 1000 bid + C 500 bid	34	6693	6	other reason (abnormal baseline lab)	not evaluable	not available
A 1000 bid + C 500 bid	34	6736	119	other reason (abnormal baseline labs)	not evaluable	not available

Table 28 presents the same results for those patients considered non-evaluable for the "intention-to-treat" patient population.

TABLE 28
Listing of Results for Patients Excluded from "Intention-to-Treat" Analysis
Study #127

Treatment Group	Site Number	AN	Discontinued Day	Reason Discontinued	*H.pylori* Status at Week 8	Duodenal Ulcer Healed Status by Week 8
O 20 bid + A 1000 bid + C 500 bid	3	6607	74	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	4	6516	60	deviation from protocol	infected†	not healed‡
O 20 bid + A 1000 bid + C 500 bid	5	6586	23	deviation from protocol	infected†	not healed‡
O 20 bid + A 1000 bid + C 500 bid	12	6676	7	deviation from protocol	infected†	not healed‡
O 20 bid + A 1000 bid + C 500 bid	17	6556	58	completed study	not infected	not healed
O 20 bid + A 1000 bid + C 500 bid	22	6645	62	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	27	6597	54	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	27	6600	54	completed study	not infected	healed
O 20 bid + A 1000 bid + C 500 bid	28	6601	-1	deviation from protocol	infected†	not healed‡
A 1000 bid + C 500 bid	24	6590	57	completed study	not infected	healed
A 1000 bid + C 500 bid	33	6689	118	completed study	not infected	healed

† *H.pylori* status at Week 8 was not evaluable, but would have been estimated as infected for the "intention-to-treat" analysis.

‡ Duodenal ulcer healed status by Week 8 was not available, but would have been estimated as not healed for the "intention-to-treat" analysis.

DEMOGRAPHIC RESULTS

There were no significant differences in demographic characteristics for either the per-protocol or the intent-to-treat populations. This includes gender, age, race, ulcer size, global ulcer symptoms, smoking status, and alcohol use.

COMPLIANCE RESULTS

There was no difference in study medication compliance between treatment groups. The percent of patients that were compliant with study medication is outlined in Table 29.

TABLE 29
Patient Compliance of Study Medication Taken
All Randomized Patients
Study #127

	O 20 bid + A 1000 bid + C 500 bid (N = 86)	A 1000 bid + C 500 bid (N = 85)
Number (%) of Patients	n (%)	n (%)
Compliant	75 (87%)	80 (94%)
Noncompliant	11 (13%)	5 (6%)

Note: There was no significant difference observed between the treatment groups, ($p>0.050$), using Fisher's Exact Test.

EFFICACY RESULTS

The sponsor's Per-protocol and Intent-to-Treat eradication rates and 95% confidence intervals are presented in Table 30.

TABLE 30
***H. pylori* Eradication at Week 8**
[95% Confidence Intervals]

Study #127

Per-Protocol Analysis	O 20 bid + A 1000 bid + C 500 bid	A 1000 bid + C 500 bid
	n/N (%)	n/N (%)
H. pylori Eradicated at Week 8	51/61 (84%)* [74% , 93%]	28/66 (42%) [31% , 54%]
By baseline smoking status		
Smokers	21/22 (95%)† [75%, 100%]	9/32 (28%) [13%, 44%]
Non-smokers	30/39 (77%) [64%, 90%]	19/34 (56%) [39%, 73%]
Intent-To-Treat Analysis		
H. pylori Eradication at Week 8	56/77 (73%) * [63% , 83%]	30/83 (36%) [26% , 46%]

Note: There was a significant interaction between baseline smoking status and treatment group ($p \leq 0.100$), using a logistic regression model in the per-protocol analysis

* Significantly different from A 1000 bid + C 500 bid ($p<0.001$), using a logistic regression model with baseline smoking status as a covariate in the per-protocol analysis

† Significantly different from A 1000 bid + C 500 bid ($p<0.001$), using a logistic regression model in the per-protocol analysis

• Significantly different from A 1000 bid + C 500 bid, ($p<0.001$), using a logistic regression model in the intent-to-treat analysis

Statistical Reviewer's Comment: Even though smoking status was stratified for at baseline, there were somewhat fewer smokers randomized to the triple therapy arm (there were 38 smokers and 48 non-smokers randomized at baseline to the triple therapy group; there were 41 smokers and 44 non-smokers randomized at baseline in the antibiotic alone arm). This slight imbalance in the triple therapy arm is further aggravated in the per-protocol analysis

by the fact that 5 smokers in the triple therapy arm have no H. pylori eradication information at the follow-up visit.

Eradication rates by demographic characteristics are presented in Table 31. Numeric differences were seen for many of these characteristics. There was a trend towards lower eradication rates in males, blacks, and smokers in the antibiotic alone arm. No clinical trends were observed in the triple therapy arm.

There were 8 patients who discontinued due to an adverse event. None of these patients had *H. pylori* assessed at the 8 week visit.

ID #	Action Taken	Treatment	AE	CAUSE	DISCON	INTENSITY
6714	Stopped Drug	Triple	STOMACH PAIN	Possibly	7	Severe
6714	Stopped Drug	Triple	DIARRHEA	Probably	7	Severe
6714	Stopped Drug	Triple	NAUSEA	Probably	7	Severe
6644	None	Dual	PNEUMONIA	unlikely	49	Moderate
6642	Stopped Drug	Triple	FATIGUE	Possibly	4	Moderate
6642	Stopped Drug	Triple	NAUSEA	Probably	4	Severe
6623	Stopped Drug	Triple	Inc DIARRHEA	Probably	64	Moderate
6592	Stopped Drug	Triple	BAD TASTE MOUTH	Possibly	16	Severe
6591	Stopped Drug	Dual	VOMITING	Probably	11	Mild
6591	Stopped Drug	Dual	NAUSEA	Probably	11	Moderate
6553	Stopped Drug	Dual	URTICARIA	Probably	11	Moderate
6535	None	Dual	Inc ABDOMINAL Pain	unlikely	12	Severe

Medical Officer's Comment: An alternative way to evaluate these patients in the per-protocol analysis is to consider them to be evaluable failures if the clinical AE was related to the study medication or thought to represent a worsening of the primary disease. In this case, patient numbers 6714, 6642, 6623, 6592, 6591, and 6553 might be considered evaluable failures because the reason for discontinuation was an AE and this AE was probably or possibly related to the study medication. Using this criteria for the per-protocol analysis, the eradication rates for the triple therapy should be 78% (51/65) and 41% (28/68) for the dual therapy.

TABLE 31
***H. pylori* Eradication at Week 8 - Subgroup Analysis**
Number (%) of Patients
Per-Protocol Analysis

Study #127

	O 20 bid + A 1000 bid + C 500 bid		A 1000 bid + C 500 bid	
	n/N (%)		n/N (%)	
Overall Eradication Rates	51/61	(84%)	28/66	(42%)
Gender				
Males	35/41	(85%)	15/43	(35%)
Females	16/20	(80%)	13/23	(57%)
Race				
Caucasian	37/43	(86%)	23/46	(50%)
Black	13/16	(81%)	4/18	(22%)
Other	1/2	(50%)	1/2	(50%)
Age				
≤ 65 years	44/52	(85%)	26/62	(42%)
> 65 years	7/9	(78%)	2/4	(50%)
Baseline smoking status				
Smokers	21/22	(95%)	9/32	(28%)
Non-smokers	30/39	(77%)	19/34	(56%)
Largest Baseline Duodenal Ulcer Size				
≤ 1 cm	46/55	(84%)	26/58	(45%)
> 1 cm	5/6	(83%)	2/8	(25%)

Note: No statistical comparisons were made between the treatment groups for these subgroup proportions.

A comparison of the three diagnostic tests is presented in Table 32.

TABLE 32
Comparison of *H. pylori* Diagnostic Methods
All Patients With Interpretable Test Results
Both Treatment Groups Combined (Study #127)

	Baseline			Week 8		
CLOtest® vs. Histology						
	Histology results			Histology results		
CLOtest® results	Positive	Negative	Total	Positive	Negative	Total
Positive	160	7	167	42	5	47
Negative	0	2	2	8	94	102
Total	160	9	169	50	99	149
McNemar's Test p-value:	not calculated			p = 0.581		
Kappa statistic: 95% CI:	not calculated			κ = 0.80 [0.70, 0.90]		
CLOtest® vs. Culture						
	Culture results			Culture results		
CLOtest® results	Positive	Negative	Total	Positive	Negative	Total
Positive	129	28	157	36	9	45
Negative	0	1	1	7	89	96
Total	129	29	158	43	98	141
McNemar's Test p-value:	not calculated			p = 0.804		
Kappa statistic: 95% CI:	not calculated			κ = 0.74 [0.62, 0.86]		
Histology vs. Culture						
	Culture results			Culture results		
Histology results	Positive	Negative	Total	Positive	Negative	Total
Positive	128	22	150	41	6	47
Negative	0	8	8	2	92	94
Total	128	30	158	43	98	141
McNemar's Test p-value:	p < 0.001 *			p = 0.289		
Kappa statistic: 95% CI:	κ = 0.37 [0.18, 0.56]			κ = 0.87 [0.78, 0.96]		

* The proportion of patients with positive test results is significantly different between the two diagnostic tests, ($p \leq 0.050$), using McNemar's test.

Medical Officer's Comment: False negative CLOtest results compared with culture and histology were 16% (7/43) and 16% (8/50), respectively at the follow-up visit.

Statistical Reviewer's Comment: Both the kappa statistics and the results from McNemar's test suggest that there is a fair amount of agreement between the various pairs of tests at Week 8.

The distribution of test results at baseline and week 8 is presented in Tables 33 and 34.